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EXAMINER	
KIM, ALEXANDER D	

ART UNIT	PAPER NUMBER
1656	

DATE MAILED: 05/16/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/812,315	RIEPING, MECHTHILD	
	Examiner	Art Unit	
	Alexander D. Kim	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *6 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above claim(s) *10-13* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/18/04,10/17/05*.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *attached* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Application Status

1. In response to the previous Office action, a written restriction requirement (mailed on March 22, 2006), Applicants filed a response received on April 6, 2006. Claims 1-12 are pending in this instant Office action.

Election

2. Applicant's election without traverse of Group I, Claims 1-9, is acknowledged. Claims 1-12 are pending in the instant application. Claims 10-12 are withdrawn from consideration as non-elected inventions.

Applicant elected the species of the thrABC operon in a response received on April 6, 2006 from the Claim 8; Applicant elected the species of the tdh gene by telephone communication on April 28, 2006 from the Claim 9 as indicated on Examiner Initiated Interview Summary PTO-413B.

Priority

3. Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d) to a foreign patent application 103 14 618.0 filed in Germany on April 1, 2003; no translation has been provided.

Information Disclosure Statement

4. Information disclosure statements (IDS) filed on 11/18/2004 and 10/17/2005

have been reviewed, and their references have been considered as shown by the Examiner's initials next to each citation on the attached copies.

Objections to the Specification

5. The specification is objected to because of the following informalities:

a. The specification is objected to because the title is not descriptive of elected claims. A new title is required that is clearly indicative of the invention to which the elected claims are drawn (see M.P.E.P. § 606.01). The examiner suggests the following new title, for example:
---Process for amino acid production using Enterobacteriaceae strain with enhanced galP encoding galactose permease---

b. In the specification, the Abstract is objected to for not completely describing the disclosed subject matter (see M.P.E.P. § 608.01(b)). It is noted that in many databases and in foreign countries, the Abstract is crucial in defining the disclosed subject matter, thus, its completeness is essential. The Examiner suggests the inclusion of the full name of the enzyme, galactose permease, and the source species, *E coli*, for completeness.

c. The abstract of the disclosure is also objected to because it is not in one paragraph. Correction is required. See MPEP § 608.01(b).

Objections to the Drawing

6. The drawings are objected to as failing to comply with 37 CFR 1.84(p)(5) because they include the following reference character(s) not mentioned in the description: "Figure. 1" labeling is missing in the drawing. Corrected drawing sheets in compliance with 37 CFR 1.121(d), or amendment to the specification to add the reference character(s) in the description in compliance with 37 CFR 1.121(b) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-9 are rejected under of 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 1 and 6 recite the limitation "the galP gene" and "another nucleotide sequence coding for galP".

There is insufficient antecedent basis for this limitation "the galP gene" in the claim. It is unclear if the claims are limited to any one gene or the endogenous gene from the specific microorganism.

Also, if the galP gene is interpreted as the gene coding for a galactose permease, another nucleotide sequence in the instant claims can be interpreted as the galactose-proton symporter gene and *vice versa*. It is unclear if the claims are limited to the galactose permease or the galactose proton symporter. The specification and claims do not limit to one enzyme (see page 6 line 17). Clarification is required.

8. Claims 4 and 5 are rejected under of 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 4 and 5 recite the limitation "the biosynthesis pathway" and "metabolic pathway", respectively. It is unclear if the claim is limited to a one particular biosynthesis pathway and which enzymes are encompassed by the term. Clarification is required.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-9 are rejected under 35 U.S.C. § 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the

inventor(s), at the time the application was filed, had possession of the claimed invention. The instant claims are drawn to a process for the production of an L-amino acid comprising fermenting an *Enterobacteriaceae* microorganism with an enhanced galP gene.

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these (Enzo Biochem 63 USPQ2d 1609 (CAFC 2002)).

The instant specification discloses overexpression of a galP gene to increase galP enzyme(s) activity, however, as noted above, the term galP is unclear. The instant specification lacks support to a specific structure by just disclosing enzyme name. The prior art also do not support a specific structure of galP enzyme. The specification lacks

any correlation between structure of the disclosed galP sequence and the function of the disclosed galactose permease. Thus one skilled in the art would not be in possession of the claimed genus of the instant specification.

10. Claims 1-5 and 8-9 are rejected under 35 U.S.C. § 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The instant claims are drawn to a process for the production of an L-amino acid comprising fermenting an *Enterobacteriaceae* overexpressing the galP gene, and additionally increasing the thrABC gene, attenuating the tdh gene expression or switching off of other genes.

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common

characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these (Enzo Biochem 63 USPQ2d 1609 (CAFC 2002)).

The instant specification discloses an E. coli that overexpresses a galP gene to increase the activity of galP by increasing the gene copy number. The breath of claims 1-5 includes using host cells having increased catalytic activity of galP (p. 7, line 1-5). Claim 8 also reads on using host cells having additional proteins with increased catalytic activity encoded by the thrABC operon. Claim 9 reads on using host cells having additional protein with decreased catalytic activity encoded by the tdh gene suggested by "enzyme or protein with a lower activity" in the specification (p. 16, line 23). The specification teaches an increase in total activity of the galactose permease by increased level of galP gene expression within a bacterium. However, the instant specification does not disclose one single example of using bacteria having galactose permease or thrABC gene with increased catalytic activity. The specification also does not disclose a single example of using bacteria having the tdh gene with reduced catalytic activity. It is unpredictable to make the galactose permease or proteins encoded from thrABC having increased catalytic activity and the tdh gene encoding protein having reduced catalytic activity because the lack of correlation between structure and function. The one skilled in the art would not be in possession of the claimed genus of the instant specification.

11. Claims 1-5 and 8-9 are rejected under 35 U.S.C. 112, first paragraph, scope of enablement, because the specification, while being enabling for a process for the producing L-amino acid using an *Enterobacteriaceae* family with an increase of galactose permease gene expression, does not reasonably provide enablement for a process for the production of L-amino acid using galactose permease with increased catalytic activity. The specification does not enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and use of the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or

unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

The nature of the invention is drawn to a process for the production of an L-amino acid using an *Enterobacteriaceae* family with overexpression of the galP gene encoding galactose permease (Claims 1-5), additionally overexpressing the thrABC gene (Claim 8) or additionally attenuating the tdh gene (Claim 9). The breadth of claims includes a method of using an *Enterobacteriaceae* having galactose permease with increased catalytic activity (Claims 1-5), additionally increased catalytic activity of protein encoded by the thrABC gene (Claim 8) or additionally decreased catalytic activity of protein encoded by the tdh gene (Claim 9). according to a disclosure of the instant specification. However, the instant specification discloses no direction or guidance on how to make any protein with increased catalytic activity or decreased catalytic activity. The specification discloses neither a single working example of a protein with increased catalytic activity or decreased catalytic activity. Additionally, the prior art does not teach as to how to make and use of a galactose permease with increased catalytic activity, increased catalytic activity of protein encoded by the thrABC gene or decreased catalytic activity of protein encoded by the tdh gene. Because of the complex nature of enzyme catalysis and number of amino acids involved in catalysis, the unpredictability of increasing catalytic activity or decreasing catalytic activity of proteins are high. For all of the above reason, it would require undue experimentation necessary to practice the full scope of claimed methods.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 1-5 are rejected under 35 U.S.C. 102(b) as being anticipated by Valle et al. (USPAP 2002/0155521 published on Oct. 24, 2002). The instant claims are drawn to a process for the production of an L-amino acid by using Enterobacteriaceae family with the galP gene overexpressed in the microorganism with additional limitations: L-amino acid is L-threonine (Claim 2), amino acid having fermentation constituents (Claim 3), a gene overexpression from the biosynthesis pathway of L-amino acid (Claim 4), a gene reduced from the metabolic pathway of L-amino acid (Claim 5).

Valle et al. teach an isolated E. coli having an increased level of the galP gene expression compared to the parent E. coli because of constitutive galactose permease expression resulting from the removal of two repressors (see p. 6, § 0057 and § 0058). Valle et al. teach using E. coli $Pts^-/glucose^+$ strain NF9/pBE7 to increase the production of tryptophan as described in Example 8, § 0099. Preparing L-trytophan by steps of removing the cells and debris by centrifugation, and analyzing the supernatant by high performance liquid chromatography (see Example 8, §0098) after growing E. coli $Pts^-/glucose^+$ strain in the media; these steps will also isolate L-threonine inherently. Also, Valle et al. specifically suggest that strains $Pts^-/glucose^+$ can be utilized for an increase in threonine production (see § 0005 and § 0044). Thus, the Valle et al. meet all the

limitation of Claim 1-3. Valle et al. also teach a method of preparing a tyrptophan evidenced by the centrifugation cell removal and analyzing supernatant (see Exmaple 6 § 0098) using the Pts^-/$glucose^+$ strain NF9 contains pRW5tkt (see Example 6, §0088), which contains "the cloned E. coli tktA gene encodes transaldolase (US Pat. No. 5,168056)". This strain overexpresses tktA gene (§0008, p. 1), which is a part of a biosynthesis pathway, thus meets the claim limitation of Claim 4. The Pts^-/$glucose^+$ strain NF9 used by Valle et al. contains inactivation of PEP-dependent phosphotransferase transport system (PTS) to reduce PEP consumed in glucose transport and redirect PEP usage "to increase production of tryptophan, phenylalanine, tyrosine and other compounds" as shown in result Table 2a (see §0005 and § 0046) thus meets the limitation of Claim 5.

13. Claims 1-2 and 6-7 are rejected under 35 U.S.C. 102(b) as being anticipated by Grossiord et al. (2003 Feb, Journal of Bacteriology, Vol. 185(3), pp. 870-878) as evidenced by Ravnikar et al. (1987, Journal of Bacteriology, Vol. 169(10), pp 4716-4721). The instant claims are drawn to a process for the production of an L-amino acid by using *Enterobacteriaceae* family with increasing copy number of the galP gene (Claim 6) and changing the promoter normally found in galP gene (Claim 7).

Grossiord et al. teach a process of increasing copy number of galP gene by constructing a plasmid pNZ8410 containing full length of galP gene (see Table 2, p. 871) and transformed into E. coli strain HB101 as described in the Results (see bottom of left column, p. 873). The E. coli of Grossiord et al. shows the expression of

polynucleotide encoded from the galP gene by showing ability to ferment galactose on MacConkey agar plates (see Results, left column, pp. 873, lines 5-6). The process of Grossiord et al. express galP gene by increasing the copy number by transformed plasmid pNZ8410 (see Table 3 and bottom of left column, p. 873) and this galP gene has a different promoter from naturally occurring gene.

Grossiord et al. teach the inherent production of L-threonine evidenced by the fermentation and centrifugation steps involved in DNA isolation as described in the Materials and Methods (pg 871, right column, line 12). Therefore, a process of Grossiord et al. meets all the claim limitations.

The constitutive production of galP protein is evidenced by Ravnikar et al. who teach E. coli transformed with pDR121. As explained in Fig. 2 of Ravnikar et al., the pDR121 is made from pBR322 containing threonine dehydrogenase between EcoRI and SalI cloning site that is the same cloning site used by Grossiord et al. Ravnikar et al. teach the expression of cloned protein in the Results pp. 4719 (left column line 10-17 and Table 3).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over Valle et al. (USPAP 2002/0155521 published on Oct. 24, 2002) in view of Debabov et al. (USP 6,132,999 published on Oct. 17, 2000).

Valle et al. teach as described above. Valle et al. does not teach overexpression of the thrABC operon.

Debabov et al. (2000) teach a process of improved amino acid by transforming an E. coli with expression vector consist of a threonine operon (thrABC), which overexpressing the thrABC gene product. Debavov et al. (2000) teach a process of making L-threonine by using E. coli BKIIM B-5318 in Example 1. The E. coli BKIIM B-5318 has "plasmid pPRT614, which has threonine biosynthesis genes (thrA, B, and C)" as disclosed in the Abstract.

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to increase expression of galP encoding galactose permease of Valle et al. and additionally overexpress thrABC operon of Debabov et al. by transforming with a expression vector consist of thrABC gene. The motivation to do so is provided by Valle et al. and Debabov et al. (2000) who teach the usefulness of increasing the production of L-amino acid in E. coli. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

15. Claim 9 is rejected under 35 U.S.C. 103(a) as being unpatentable over Valle et al. (USPAP 2002/0155521 published on Oct. 24, 2002) in view of Debavov et al. (USP 5,705371 published on Jan. 6, 1998).

Valle et al. teach as described above. Valle et al. does not teach attenuation of the tdh gene.

Debavov et al. (1998) teach a process of making L-threonine by attenuation of the tdh gene encoding a threonine dehydrogenase. Debavov et al. (1998) teach "E. coli strain VNIIgenetika 472T23" having "insertion of transposon Tn5 into gene tdh " "devoid completely of activity" of a threonine dehydrogenase (see column 2, line 53-59)

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made by increasing expression of a galP encoding galactose permease of Valle et al. and additionally attenuating the tdh gene of Debavov et al. (1998). The motivation to do so is provided by Valle et al. and Debabov et al. (1998) who teach the usefulness of increasing the production of L-amino acid in E. coli. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

Additional References

16. The following are cited to complete the record but is not prior art:

a) Hernandez-Montalvo et al (SEP 20, 2003) Expression of galP and glk in a Escherichia coli PTS Mutant Restores Glucose Transport and Increases Glycolytic Flux to Fermentation Products, Biotechnology And bioengineering, Vol. 83-6, pp. 687-694.

Conclusion

17. Claims 1-9 are rejected for the reasons identified in the numbered sections of the Office Action. Applicants must respond to the objections/rejections in each of thenumbered sections in the Office action to be fully responsive in prosecution.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alexander D. Kim whose telephone number is (571) 272-5266. The examiner can normally be reached on 8AM-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached on (571) 272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Alexander Kim
May 1, 2006

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SUPERVISORY PATENT EXAMINER